



Treatment of Hypertension

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INTENDED LEARNING OBJECTIVES (ILO)



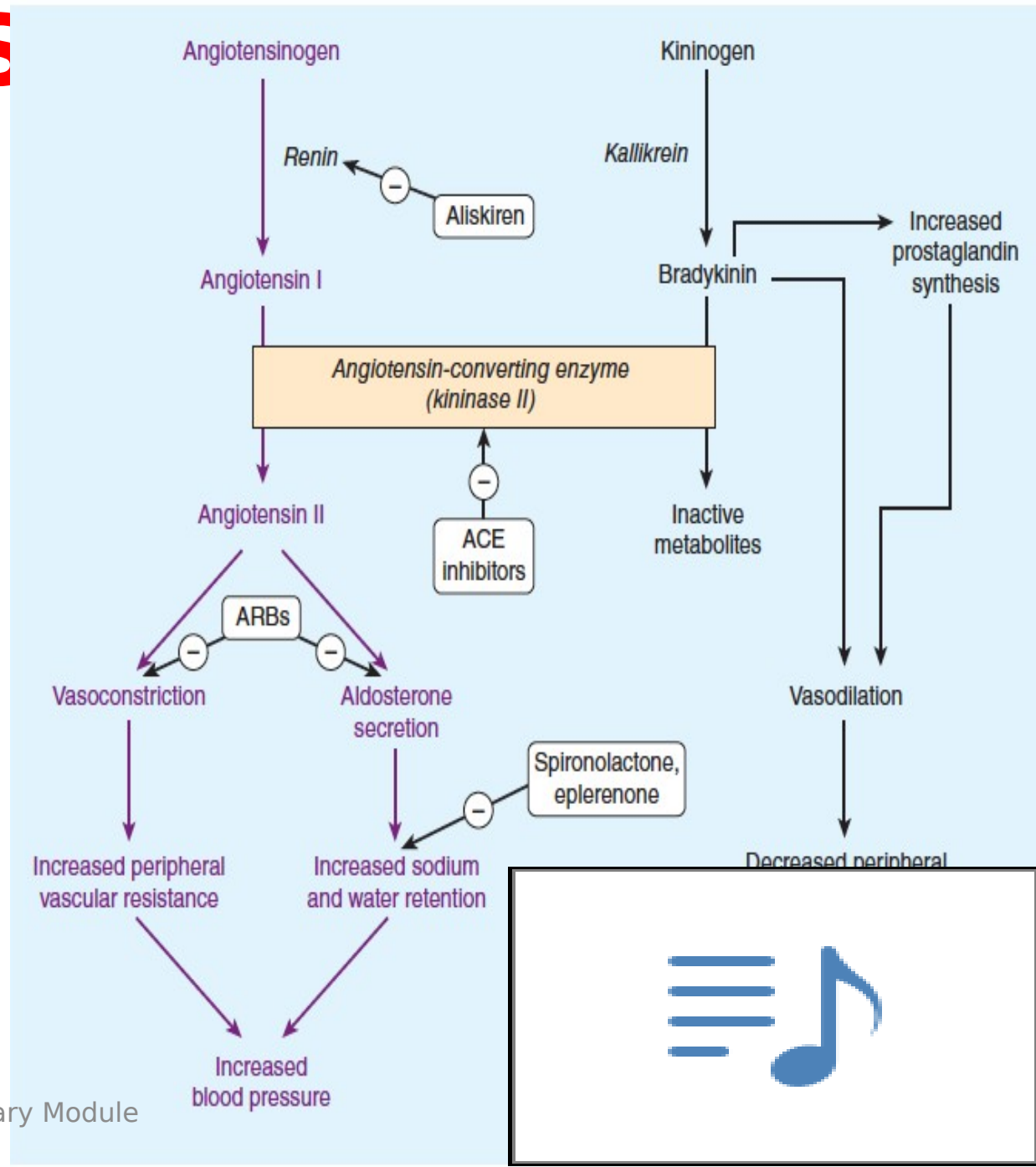
Lecture 2:

1. Explain the mechanism of action of anti-hypertensive drugs acting through the renin-angiotensin system
2. List the uses, adverse effects of ACEIs
3. Explain the role of calcium-channel blockers as antihypertensive drugs
4. Identify the 3 classes of calcium-channel blockers.



3. ACE INHIBITORS

- They **inhibit the converting enzyme peptidyl dipeptidase** that hydrolyzes angiotensin I to angiotensin II and (another name of the enzyme is plasma kininase).
- it also **inactivates bradykinin**, a potent vasodilator).
- The hypotensive activity of captopril results both from **an inhibitory action** on the renin-angiotensin system and a **stimulating action** on the kallikrein-kinin system.
- **They do not result in reflex sympathetic activation** and can be used safely in persons with ischemic heart disease.
- Cardiac output and heart rate **are not significantly changed**.



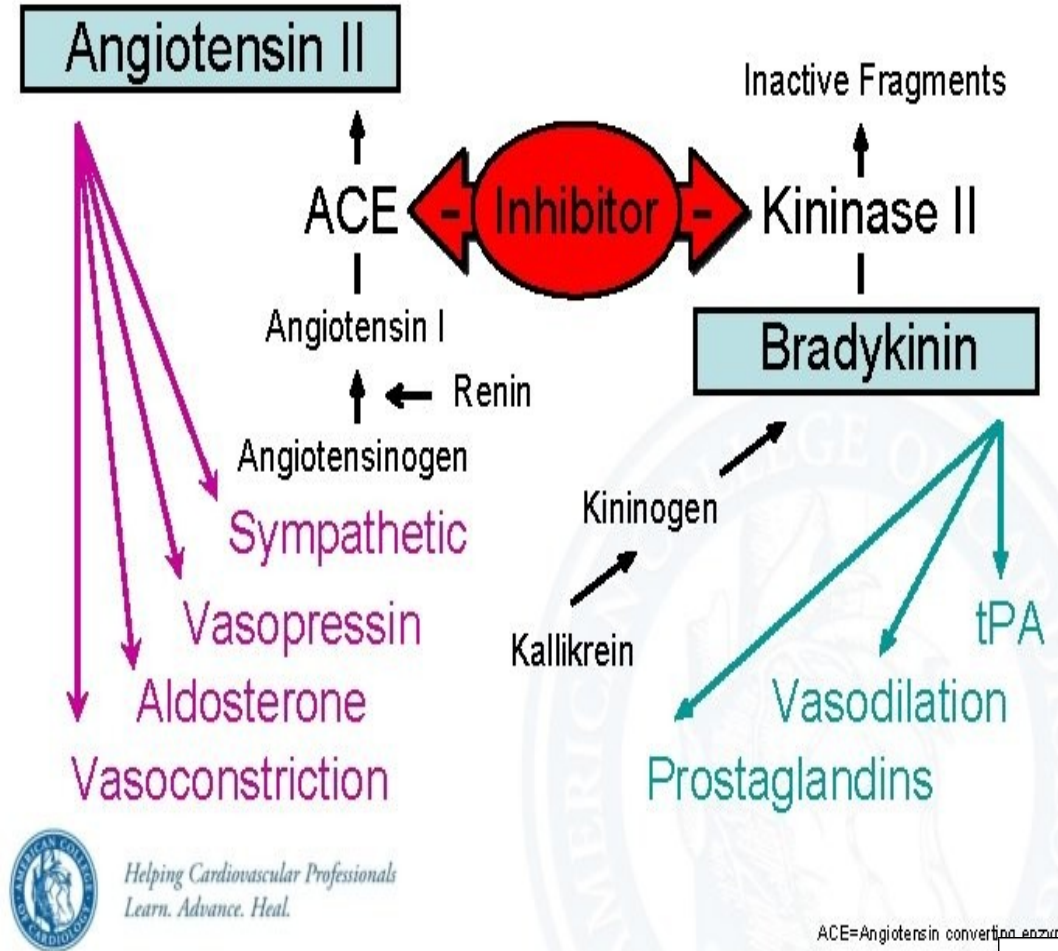
Inhibitors (Action)

ACE Inhibitor: Mechanism of Action

Inhibitor Conversion of inactive to active Enzyme

- a) Decrease VC.
- b) Decrease Aldosterone (--Na + / fluid retention).
- c) Inhibit Sympathetic activation.
- d) Decrease Hypertrophy & Remodeling of heart & BV
- e) Increase Renin & Angiotensin I.

2- Decrease Inactivation of Bradykinin (BK):



Pharmacological Actions of ACEIs

a- **Mixed VD**: Arterio & Venous.

b- Arterio. VD decrease T.P.R.: decrease After-load & BP

c- Weak Vein. VD: decrease V.R. ,, decrease E.D.V. ,, decrease Pre-load & BP.

d- **C.O.P. is maintained**

e- Increase renal blood flow BUT decrease glomerular filtration rate (GFR) , (Efferent VD), decrease Glomerular hypertension.

f- Advantages:

- NO decrease of COP, even it may increase COP in HF.
- NO postural hypotension (Less Veno-dilator)
- NO reflex tachycardia (decrease Baroreceptors reflex & Sympathetic activity).
- NO abnormality in Glucose or Lipid or Cholesterol or Uric acid metabolism



Therapeutic Uses of ACEIs:

a- Hypertension, especially:

- High renin.
 - Diabetic nephropathy because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure). .
- These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure.
- Heart failure.
 - But Not effective in Primary Hyperaldosteronism.

b- Heart Failure:

- Decrease both After & Preload: Improve cardiac performance and increase COP.
- Decrease Secondary hyperaldosteronism : Natriuretic : decrease edema.



Classification of ACEIs

1- S-H Containing ACEIs

Captopril

- Active drug.
- Well absorbed orally, BUT affected by food. Taken 1-2 hours before meal.
- Does not pass BBB.
- 50% metabolized in liver & 50% excreted unchanged in urine.
- Short acting. Used twice or thrice per day.
- Frequent side effects e.g. Angio-edema.



2- Non-S-H Containing ACEIs

- Less side effects than Captopril.
- Longer $t_{1/2}$, used once or twice per day.
- Oral absorption is not affected by meal.

A) Active Drugs:

Lisinopril: Active drug. NOT metabolized → Longest $t_{1/2}$, used once daily..

B) Prodrugs

→ Metabolism → Active metabolites.

Enalapril → Enalaprilat available ampoule for injection

Perindopril → Perindoprilat

Benazepril → Benazeprilat

Ramipril → Ramiprilat

Quinapril

Fosinopril: Excreted in bile, not urine. Its dose has not to be readjusted in impaired renal function. As, Most of ACE inhibitors are eliminated primarily by the kidneys; **doses of these drugs should be reduced in patients with renal insufficiency**



Side Effects of ACEIs

Cough

H.A.E = C1E Inhibitor Deficiency ↑ Bradykinin Levels

**Dry and
irritant
Treat by
NACID**

Angioedema → History of Angioedema/Anaphylaxis

Pregnancy Problems → Pregnancy

**Fetal hypotension, renal failure,
Oligohydramnios, Malformation**

Taste Changes (Dysgeusia)

Other (Rash, Fatigue)

Proteinuria → B/L Renal Artery Stenosis

Renal Insufficiency → B/L Renal Artery Stenosis

**Fatal Renal
Failure.**

Increased Potassium → Hyperkalemia

**especially if accompanied with
K⁺-retaining diuretics e.g.**

Low Blood Pressure → **especially in Na⁺-depleted patients by diuretics.**

**Treat by Saline. Stop diuretics before
the use of ACEI.**



Drug Interactions of ACEIs

- a- Na⁺-depleting diuretics accentuates the initial hypotensive effects.
- b- K⁺-retaining diuretics e.g. Spironolactone augments the hyperkalemia effect.
- c- NASID e.g. aspirin antagonize partially the hypotensive effect by blocking synthesis of PGs.



4. Angiotensin II (AT1) - Receptor Blockers

Members : Losartan, Valsartan, Candesartan, Telmisartan and Irbesartan

Non-peptide:

- **Compete with Angiotensin II for AT1-receptors.**
- **They are Pure antagonists.**

Pharmacologic effects of ARBs are similar to those of ACE inhibitors in that they produce:

a- Decrease V.C: V.D -They also release prostacyclin: VD.

b- Decrease Synthesis and release of Aldosterone

c-Inhibit Sympathetic activation: Block of presynaptic AT1-receptors on adrenergic neurons: decrease Noradrenaline release.

d-Prevent hypertrophy & Remodeling of Heart & BV due to hypertension.

Metabolic Actions: decreases Glomerular hypertension (Effluent retaining V.D) effect correct Hypokalemia.

Therapeutic Uses: Similar to ACEIs Effective orally.

Side Effects: Similar to ACEIs **BUT although the risk angioedema are significantly decreased.**



5. Renin Inhibitor

I. ↓ release:

- ❑ A selective renin inhibitor, **aliskiren**
- ❑ Aliskiren directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than do ACE inhibitors or ARBs. **As it blocks the rate-limiting step of the renin-angiotensin-aldosterone system (RAAS).**
- ❑ It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- ❑ Aliskiren can also cause cough and angioedema but probably less often than ACE inhibitors.
- ❑ Aliskiren is contraindicated in pregnancy.
- ❑ Aliskiren should be prescribed with caution for patients with moderate renal dysfunction.

II. Renin receptor blockers:

- ❑ e.g enalkiren, remikiren





6. Calcium-Channel Blockers

Classes

- The calcium-channel blockers are divided into three chemical classes

1. Diphenylalkylamines:

- ***Verapamil***
 - Has effects on both cardiac and vascular smooth muscle cells.
 - Its effect on the heart is more pronounced than its effect on blood vessels.
 - It inhibits cardiac properties and so produces bradycardia and it produces weak V.D.
 - Due to inhibition of cardiac properties, it is used to treat arrhythmias



2. Dihydropyridines:

- ***Nifedipine: amlodipine, felodipine, isradipine, nicardipine, and nisoldipine.***
- Affects vascular smooth muscle more than the cardiac muscle.
- Cause vasodilatation with minimal effect on the heart.
- Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines.

3. Benzothiazepines:

- ***Diltiazem:***
 - Affects both cardiac & vascular smooth muscle equally.
 - Causing negative inotropic effect and V.D.



Therapeutic uses of calcium-channel blockers:

- These agents are useful in the treatment of hypertensive patients who also have
 - asthma,
 - diabetes, OR
 - angina.

Adverse effects and contraindications of calcium channel blockers

1. Dizziness, headache, and a feeling of fatigue
2. *Verapamil should be avoided in patients with congestive heart failure or with atrio-ventricular block due to its negative inotropic and dromotropic effects.*
3. *Nifedipine has caused gingival enlargement.*



Mention **THREE** adverse effects of **ACE inhibitors**.

Mention 3 classes of channel blockers



SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer
2. Neal L. Benowitz, MD. In: Katzung BG (ed.). (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.